



# Guidelines for reduction of nitrosamine and transition metal contamination in pharmaceuticals

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<b>Lead Authors</b>	Paula Kiuru, Timo Repo, Jari Yli-Kauhaluoma
<b>Contributors</b>	Paula Kiuru (UH), Sarah Seefried (UH), Nikita Slesarchuk (UH), Ellen K. Lamme MSc. (RIVM), dr. Arnout P.T. Hartendorp (RIVM), Laura Mulder, BSc. (RIVM)
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<b>PU</b>	Public, fully open, e.g., web (Deliverables flagged as public will be automatically published in CORDIS projects.)	<b>X</b>
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ACRONYM/ABBREVIATIONS	
<b>CA</b>	Consortium Agreement (contractual document between members of the consortium)
<b>DoA</b>	Description of Action (technical annex to the Grant Agreement)
<b>EC</b>	European Commission
<b>EU</b>	European Union
<b>FTP</b>	Funding and Tenders Portal: <a href="https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/home">https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/home</a>
<b>GA</b>	Grant Agreement (contractual document between EC and beneficiaries)
<b>IPR</b>	Intellectual Property Rights
<b>KO</b>	Kick Off (meeting)
<b>MC</b>	Management Coordinator
<b>MTA</b>	Milestones Trend Analysis
<b>PC</b>	Project Coordinator
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## ABSTRACTS

The presence of nitrosamine and transition metal contaminants in pharmaceuticals is a significant concern due to their potential health risks. Nitrosamines are probable human carcinogens, while excessive levels of transition metals can lead to toxicity. This deliverable outlines the guidelines for the assessment, and reduction of these impurities in medicinal products to ensure regulatory compliance.

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# 1 EXECUTIVE SUMMARY

The presence of nitrosamine and transition metal contaminants in pharmaceuticals is a significant concern due to their potential health risks. Nitrosamines are probable human carcinogens, and excessive levels of transition metals can lead to toxicity. This deliverable outlines the methods for the assessment and reduction of these impurities in active pharmaceutical ingredients (APIs).

The objectives are to reduce transition metal contamination (e.g., palladium, nickel, iridium) via flow chemistry and/or by developing new types of non-metallic catalysts, and to investigate the ways how to reduce nitrosamine contamination.

For the investigation of nitrosamine contamination, a carcinogen-free and metal-free synthesis route for irbesartan was selected. Irbesartan, an angiotensin II receptor antagonist, has suffered from nitrosamine contamination in its synthesis. The synthesis route for irbesartan has been improved to avoid the formation of nitrosamines and the use of transition metals. Additionally, harmful chlorinated solvent has been replaced with a green solvent, 2-methyltetrahydrofuran, derived from renewable sources. It has been demonstrated that nitrosamine impurities, can be detected at early stages of the synthesis route.

A novel metal-free hydroborylation method has been developed using  $C_6F_5BH_2 \cdot SMe_2$  catalyst for various C-C double bonds. It works excellently for both terminal and intramolecular alkenes. While 9-BBN works well with ester functionalities,  $C_6F_5BH_2 \cdot SMe_2$  tolerates a wide spectrum of different functional groups, including halogens and TMS-protected alcohols. This has been demonstrated using several model substrates, including terpenes and steroids.

The combination of metal-free hydroborylation and transborylation has proven to be a promising strategy for preparing air- and moisture-stable pinacolboranes. This scalable method addresses the need for a robust synthesis protocol for preparing boronic esters from simple, inexpensive alkenes for the pharmaceutical industry.

In conclusion, this study presents advancements in reducing harmful contaminants in APIs through innovative chemistry approaches, enabling safer medicinal products and compliance with regulatory standards.

## 2 DESCRIPTION OF THE DELIVERABLE OBJECTIVE AND CONTENT

In this Deliverable, the objective is to reduce transition metal contamination (e.g., Pd, Cu, Ni, Ir; quality concern) via flow chemistry and/or by developing new types of non-metallic catalysts. Next to transition metal contamination, also the investigation of nitrosamine contaminations was an objective. This work is part of Task 3.3 Reduced contamination. The *N*-nitrosodiisopropylamine (NDiPA) formation from commonly used base diisopropylethylamine (DIPEA) in the presence of a trace of acid was selected as an example.

The UH team selected to investigate the preparation of vaborbactam (a non- $\beta$ -lactam cyclic boronic acid  $\beta$ -lactamase inhibitor) in batch/flow to reduce transition metal (copper, iridium, nickel) contamination that hampers its current synthesis. Lewis acidic boron hydrides were studied as metal-free catalysts for the desired boronic esters.

A development of carcinogen-free and metal-free synthesis route for irbesartan was selected for the investigation of nitrosamine contaminations. Irbesartan is an angiotensin II receptor antagonist, whose synthesis has suffered from nitrosamines.

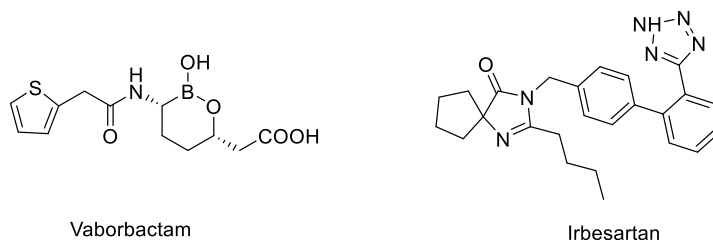


Figure 1: Structures of vaborbactam and irbesartan.

### 3 BRIEF DESCRIPTION OF THE STATE OF THE ART

#### Nitrosamines

In 2018, the presence of carcinogenic nitrosamine *N*-nitrosodimethylamine (NDMA) was detected in certain batches of the antihypertensive drug valsartan [1-2]. This discovery led to widespread recalls of valsartan products globally. Subsequent investigations revealed that the contamination was due to changes in the manufacturing process, specifically modifications in the synthesis of the active pharmaceutical ingredient (API). Nitrosamine impurities were also found in several other drugs, including other sartans, ranitidine, and metformin. Earlier tetrazole moieties present in sartans, and azide reagents used in their synthesis were thought to be the main cause for the nitrosamine contamination, but compared to secondary or tertiary amines, tetrazoles are generally considered to have a lower intrinsic risk for forming nitrosamines. Secondary and tertiary amines are more reactive towards nitrosating agents, leading to the formation of nitrosamines through well-documented pathways.

Secondary and also tertiary amines are shown to produce nitrosamines in acidic conditions, and the optimum pH for nitrosamine formation is around 3. [3] The proposed mechanism of formation of *N*-nitrosodiisopropylamine (NDiPA) is presented in Figure 2. The reaction is slower in tertiary amines, since a slow dealkylation step is part of the reaction mechanism. Traces of  $\text{NO}^+$  from water or other sources can lead to the contamination.

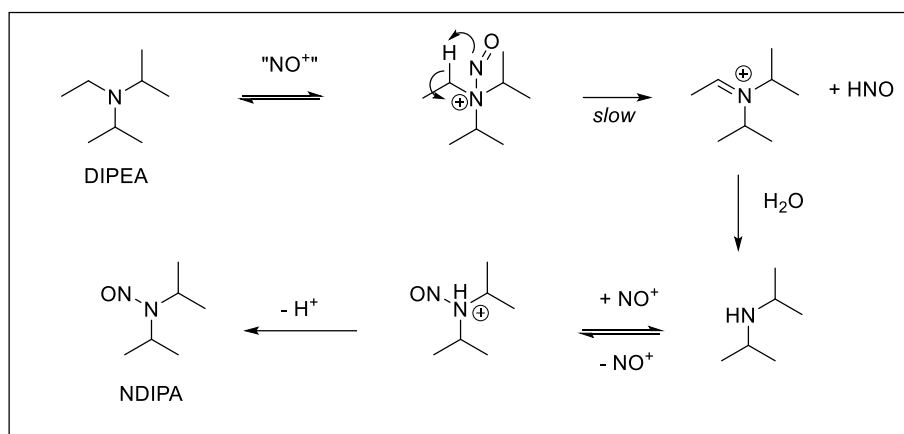
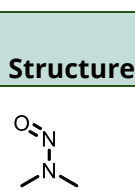
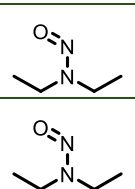
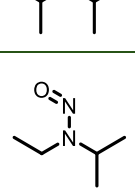
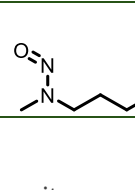
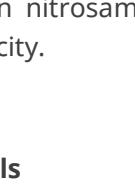


Figure 2: Proposed mechanism of NDiPA formation according to Ashwort et al.[3]

After planning of the TransPharm proposal, several scientific articles have been published dealing with nitrosamine contamination [4-6] including the whole *OPR&D* Special Issue “Nitrosamines: Challenges in Process Chemistry” in 2023 [7]. The FDA and EMA guidelines [8-9] have been issued for detecting and mitigating nitrosamine impurities, emphasizing the need for rigorous quality control and changes in manufacturing practices. The detection of nitrosamines has prompted significant changes in the pharmaceutical industry. Manufacturers are now required to assess their processes for potential nitrosamine formation and contamination. This includes evaluating raw materials, solvents, and reagents, as well as implementing stringent testing protocols. In

November 2023, the European Pharmacopoeia Commission approved the strategy for *N*-nitrosamine impurities in individual monograph European Pharmacopoeia [10], and it has been used in this Task 3.3, also in 2024 six recommended analysis methods for sartans were added to the the FDA list [11].

Table 1: Most common nitrosamine impurities from the reagents and solvents [1,4].

Compound	Structure	Origin	Daily Acceptable Intake (ng/day)
NDMA		Dimethylamine from DMF	96
NDEA		Diethylamine from TEA or DMF	26.5
NDiPA		Diisopropylamine from DIPEA	26.5
NEiPA/NiPEA		Ethylisopropylamine from DIPEA	26.5
NMBA		4-(Methylamino) butanoic acid from NMP	96

For less common nitrosamines the limits are set on a case-by-case basis, considering their potency and toxicity.

### Transition metals

The importance of boronic esters in pharmaceutical synthesis is largely associated with their role as transmetalation agents in Suzuki couplings - a crucial step in the production of various medications, including benzodiazepines, angiotensin receptor blockers or nonsteroidal anti-inflammatory drugs [12]. Moreover, boronic acid derivatives capable of inhibiting  $\beta$ -lactamase enzymes provide a promising strategy to tackle the increasing resistance of bacteria towards conventional  $\beta$ -lactam antibiotics such as penicillin [13]. The widespread application and potential of boronic esters in medicinal chemistry underscore the necessity of developing a sustainable synthetic protocol for producing them from simple, cheap alkenes.

Transition metals have long been prized in catalysis for their ability to facilitate various chemical transformations. As of 2016, more than 60% of the processes of C-C bond formation in medicinal chemistry are manifested using the Suzuki-Miyaura type of cross-coupling, which relies heavily

on transition-metal catalysis [14]. However, the use of transition metals is not without its shortcomings. One of the primary challenges is the cost associated with these metals and their ligands. Furthermore, many transition metals are inherently toxic, posing significant risks to human health and the environment [15]. The pharmaceutical industry faces the daunting task of removing trace metal residues from final products [16]. Additionally, the sensitivity of many metal catalysts to moisture and air further complicates their application, demanding stringent conditions that are not always feasible or sustainable. Thus, the reliance on transition metals does not fully align with the principles of sustainable development, which call for more environmentally benign and cost-effective alternatives [15].

In response to the limitations posed by transition-metal catalysis, there has been a growing interest in developing metal-free approaches. Metal-free reactions offer a promising solution to the challenges associated with metal catalysts, effectively circumventing their inherent disadvantages [15]. With its low atomic weight and unique chemical properties, boron has emerged as a viable alternative to transition metals in catalysis. Its ability to mimic the catalytic behavior of metals, combined with its non-metallic nature, positions boron as an attractive candidate for the core element of the catalyst, which is aligned with sustainable and green chemistry applications [17]. This shift towards metal-free methodologies is particularly appealing in the pharmaceutical industry, where strict regulations on metal content in final products necessitate the exploration of alternative synthetic routes. The synthesis of novel boron-based catalysts represents a significant advancement in the current state of the art.

One of the most promising applications of metal-free catalysis is the formation of pinacol boronic esters from alkenes. Boronic esters are highly valued building blocks in the pharmaceutical industry due to their air-stability and practicability combined with versatile subsequent transformation [18]. Traditional methods for synthesizing boronic esters often rely on transition-metal catalysis, which again has its limitations [19]. The development of metal-free approaches for the synthesis of boronic esters is thus a priority in sustainable chemistry. Hydroboration of double bonds is a concise and atom-economical reaction that holds significant potential for metal-free synthesis. Despite the numerous advantages of metal-free catalysis, the literature still lacks efficient procedures for forming pinacol boronic esters from alkenes [20-21]. The transborylation step, which involves the transfer of a boron moiety to an alkene, remains a crucial aspect of this transformation that mimics the property of a transition-metal catalyst (Figure 3). Ongoing research in this area continues to explore innovative strategies for overcoming these challenges, intending to develop robust, metal-free synthetic routes that align with the principles of green chemistry and sustainable development.

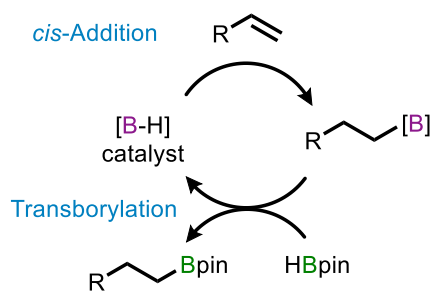


Figure 3: General mechanism of the metal-free hydroboration using transborylation approach.

## 4 DEVIATION FROM OBJECTIVES AND CORRECTIVE ACTIONS

The original scale of 300 mg for the synthesis was not enough for the nitrosamine testing in RIVM after the purification, so the reactions needed to be repeated on a 1-gram scale, which delayed the deliverable D3.4 from M24 to M33. The samples were sent to RIVM in M30 as crude products without purification as suggested by the industrial partner Orion.

## 5 INNOVATION BROUGHT AND TECHNOLOGICAL PROGRESS

### Transition metal-free synthesis of boronic esters (UH)

Our objective was to reduce transition metal contaminations in the synthesis of vaborbactam [22]. In this respect, we were aiming to render the iridium catalyst in step I (Figure 4) obsolete by developing an efficient metal-free-alkene hydroboration procedure. The following steps II-IV are transition metal-free, step II being an  $ZnCl_2$  assisted Matteson reaction [23].

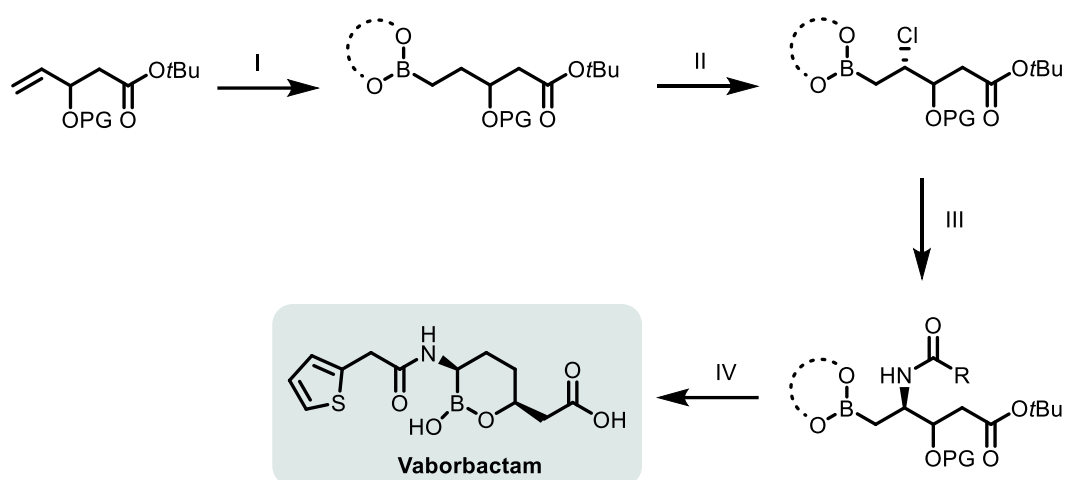


Figure 4: Schematic representation of the reported synthesis of vaborbactam. I:  $[Ir(COD)Cl]_2$ , dppb, HBPIn, DCM, II:  $n-BuLi$ ,  $ZnCl_2$ , DCM,  $-95^\circ C$ , THF, III: 1. Li-HMDS, THF,  $-78^\circ C$  to RT, 2.  $RCO_2H$ , EDCI, HOBT, NMM, DCM, IV: 3 M HCl, 1,4-dioxane, reflux.

The focus was set on developing a completely metal-free procedure for the synthesis of boronic esters from non-activated alkenes. However, commercially available pinacol and catechol borane (HBCat) do not react directly with alkenes, so we focused on developing a straightforward method that would replace previous transition metal catalysts. Recently, as shown by us and others, frustrated Lewis pairs (FLPs) can be used to functionalize unsaturated organic substrates with boron-containing reagents [24-25] and indoles can be borylated with simple boron halides [26-29]. Also, highly acidic triarylborates, such as  $B(C_6F_5)_3$  and *tris*(2,4,6-trifluorophenyl)borane, can catalyze the hydroboration of alkynes, styrenes and nitriles [20, 30-31]. Transborylation has also emerged as a purely boron-based strategy, undergoing rearrangement reactions *via*  $\sigma$  bond metathesis for the installation of a targeted boron group onto C, O, N, F and S atoms [32].

When investigating potential hydroborylation agents that can directly react with the C-C double bond, 9-BBN (9-borabicyclo[3.3.1]nonane) proved very interesting in preliminary experiments due to its reactivity. Based on our studies with 1-hexene as the first model substrate, we developed a protocol for metal-free hydroboration using 9-BBN in a catalytic amount of 10 mol% in combination with 1.1 eq of catecholborane. The terminal alkene is fully reduced after 20 h at  $70^\circ C$ , and 2-methyltetrahydrofuran can be used as a renewable solvent.

Mechanistic studies at room temperature show that the highly reactive 9-BBN initially reduces the alkene under the formation of the trialkylborane **2a<sup>#</sup>** (**Figure 5**). This is followed by a transborylation step with catechol-borane, in which the catalytic 9-BBN is regenerated and the targeted boronic ester **2a** is obtained. The hydroboration step proceeds faster than the transborylation.

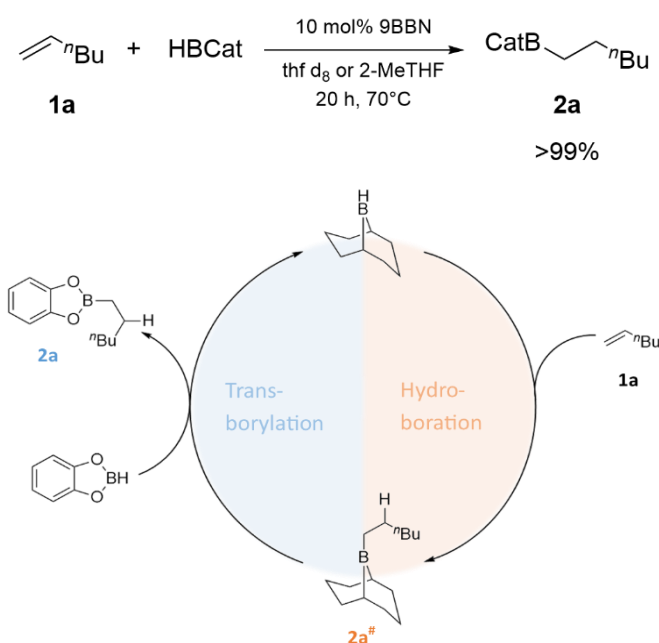


Figure 5: Reaction conditions and proposed mechanism.

The reaction scope: Under optimised conditions A for 1-hexene, terminal alkenes **1a** and **1d** can be reduced in good yields (**Figure 6**). However, the presence of an ester functionality in **1c** reduced the conversion, while steric bulk, in the proximity of the double bond in **1b**, led to a challenge in catalytic activity. Furthermore, internal alkenes gave insufficient conversions of around 30%. Hence, we varied the conditions by increasing the amount of HBCat or 9-BBN. Gratifyingly, condition **B** enabled the complete conversion of internal alkene **1g**. The steric bulk of 9-BBN was seen as challenging in view of the reactivity, e.g. in the hydroborylation of substrate **1b**, and we decided to modify the catalyst structure further.

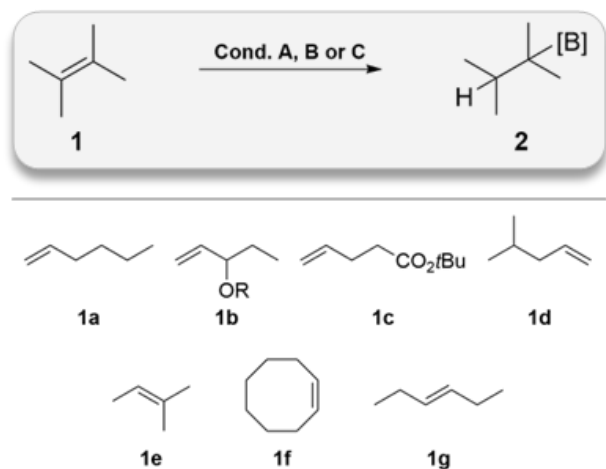


Figure 6: Substrate screening.

R = Si(Me)<sub>2</sub>tBu. Conditions:

A: 10 mol%, 9BBN, 1.1 eq. HBCat, 70 °C, 20 h, d<sub>8</sub>-THF

B: 10 mol%, 9BBN, 2.2 eq. HBCat, 70 °C, 20 h, d<sub>8</sub>-THF

C: 20 mol%, 9BBN, 1.1 eq. HBCat, 70 °C, 20 h, d<sub>8</sub>-THF

Entry	Substrates	Condition s	Conversion
1	1a	A	> 99%
2	1b	A	20%
3	1c	A	46%
4	1d	A	80%
5	1e	A	31%
6	1f	A	23%
7	1g	A	34%
8	1g	B	>99%
9	1g	C	83%

We conducted further studies on catalyst development and introduced C<sub>6</sub>F<sub>5</sub>BH<sub>2</sub>·SMe<sub>2</sub> as a new catalyst for alkene hydroboration. This compound combines a boron center with high electrophilicity and steric accessibility. We applied another series of different substrates to expand the catalytic potential of this catalyst (**Figure 7**). Our findings indicate that the reaction performs good yield with 4-chloromethylstyrene (**1b**), showing good tolerance with chlorobenzyl group. Notably, the reaction exhibited good tolerance not only with TBS-protected alcohols (see previous report) but also with simple TMS-protected (**1c**), thereby broadening the utility of the metal-free reaction for alcohol-protected substrates. Furthermore, this method has a good chemoselectivity towards terminal double bonds in the presence of an internal one (**1d**) [33].

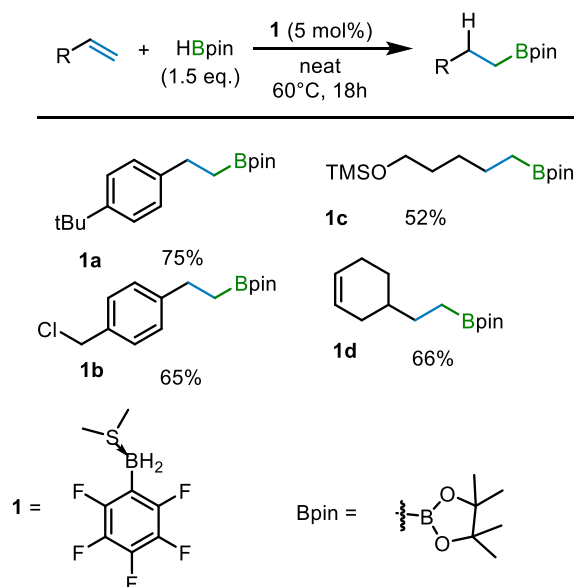


Figure 7: Hydroboration of selected terminal alkenes with C<sub>6</sub>F<sub>5</sub>BH<sub>2</sub>-SMe<sub>2</sub>

In subsequent experiments, hydroborations of various 1,1-disubstituted and internal alkenes were further studied (**Figure 8**). Surprisingly, chloride in an allyl position remained unaffected, yielding borylated methallyl chloride (**2a**) with a high yield of 96%. Additionally, 1,1-diphenylethylene also can hydroborate under these conditions (**2b**). The C<sub>6</sub>F<sub>5</sub>-substituted styrene produces different regioisomers (**2c**). We assume the strong electron-withdrawing effect of the perfluoro aromatic core also makes the Markovnikov addition feasible. 1,1,2-Trisubstituted substrate was also amenable to hydroboration, however diastereoselectivity remains challenging (**2d**) [33].

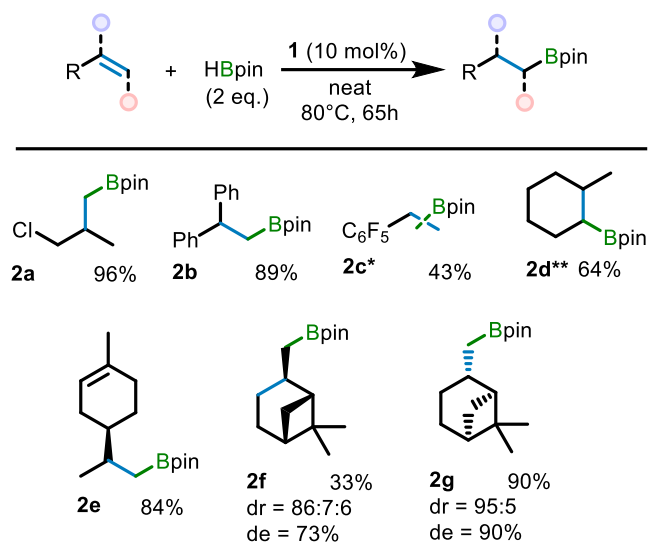


Figure 8: Hydroboration of various internal alkenes with C<sub>6</sub>F<sub>5</sub>BH<sub>2</sub>-SMe<sub>2</sub>.

To further explore the potential of the developed metal-free hydroboration concept, we screened different enantiomerically pure terpenes to ascertain whether stereoselectivity could be achieved. *R*-(+)-limonene gives 84% yield, resulting in the formation of two diastereomers (**2e**). In contrast,  $\alpha$ -(+)-pinene and  $\beta$ -(-)-pinene gave 33% (**2f**) and 90% (**2g**) yields, respectively, with one main diastereomer dominating the product profile (dr and de were calculated based on GC-MS profile). Apparently, the bulkiness of pinenes appeared sufficient to favour the formation of a single major product, whereas prochiral carbon with methyl group in *R*-(+)-limonene cannot provide enough bulkiness to ensure stereospecificity [33].

The applicability of the developed hydroboration method was further demonstrated by the borylation of a natural product derivative, pregnenolone (**3**) (**Figure 9**). Following reported procedures [34], we synthesized the pregnenolone derivative **3**. Despite an OTBS-substituent and an internal C-C  $\pi$ -bond, compound **4** was isolated with a 71% yield, showing high functional group tolerance and chemoselectivity [33].

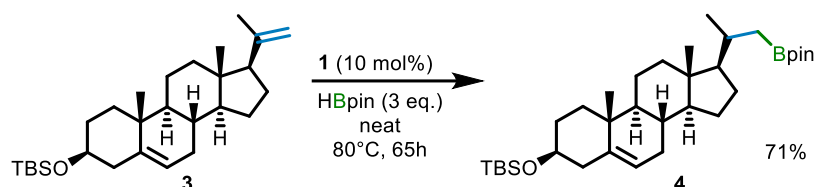


Figure 9: Hydroboration of pregnenolone derivative (**3**).

### Synthesis of irbesartan (angiotensin II receptor antagonist) (UH):

Improvement of irbesartan synthesis route to avoid formation of nitrosamines and usage of transition metals. The main focus was set to optimize the first two steps of synthesis where the most likely formation of the nitrosamines happens (Figure 10-Figure 12). Originally the first step used nickel reagent  $[\text{Ni}(\text{cod})_2]$  (Figure 10) [35], and that was tried to eliminate starting from amide coupling of 2-(*p*-tolyl)benzoic acid (Figure 11 and Table 2) using green bases and solvents [36].

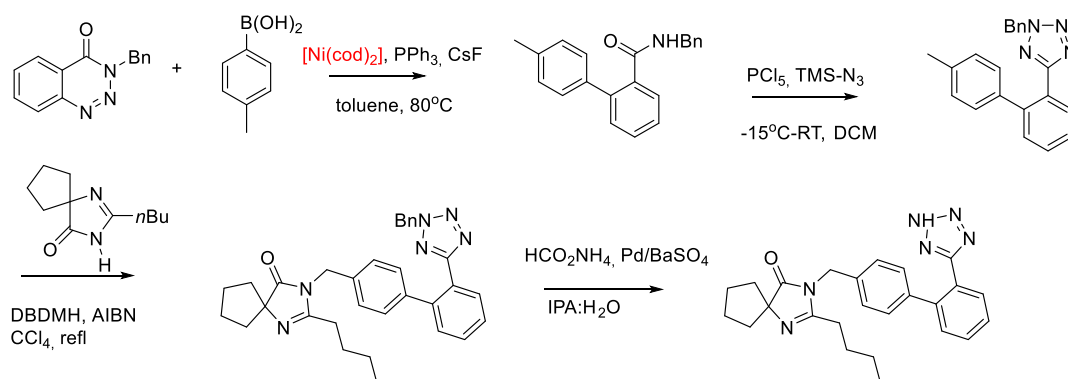


Figure 10: Literature synthesis of irbesartan [35]

Impurities from HATU as an additive made the purification fail, and in general the low yields from the first step prevented the optimization of next step in the beginning. Since the direct amide coupling reaction gave poor yields, the second approach via an acid chloride was evaluated (Figures 11 and Figure 12 and Tables 2 and 3).

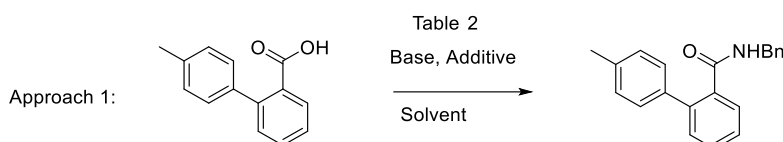


Figure 11: First step of the route of irbesartan precursors: Approach 1.

Table 2: Conditions for amide coupling (Approach 1 Figure 11)

Base	Coupling reagent	Solvent	Method <sup>a</sup>	Yield
2-picoline	HATU	2-MeTHF	rt, 20 h	Purification failed
2-picoline	HATU	2-MeTHF	MW, 2 h, 60 °C	Purification failed
2-picoline	EDC-HCl	2-MeTHF	MW, 4 h, 60 °C	7-9%
2-picoline	CDI	2-MeTHF	MW, 2 h, 60 °C	9%
DBU	CDI	2-MeTHF	MW, 2h, 60 °C	1% (failed due expired CDI)
1,1,3,3-tetramethylguanidine	CDI	2-MeTHF	MW, 2h, 60 °C	11%
DIPEA	CDI	2-MeTHF	MW, 2h, 60 °C	18%
DIPEA	CDI	2-MeTHF	MW, 2 h, 60 °C	Crude UH-1
2-picoline	-	2-MeTHF	MW, 2 h, 60 °C	Crude UH-2

<sup>a</sup> Reactions performed with 300 mg of 2-(*p*-tolyl)benzoic acid scale.

HATU (hexafluorophosphate azabenzotriazole tetramethyl uranium), MW (microwave), EDC-HCl (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide), CDI (1,1'-carbonyldiimidazole), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), 2-MeTHF (2-methyltetrahydrofuran)

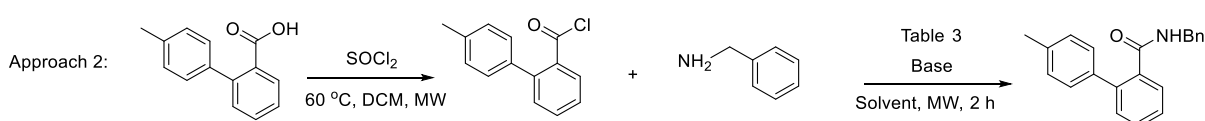


Figure 12: First step of the route of irbesartan precursors: Approach 2.

Changing the starting material from a carboxylic acid to an acid chloride with  $\text{SOCl}_2$  and then amide coupling with benzyl amine gave much better yields, and it also worked well in 2-MeTHF and with tetramethylguanidine as a base (Figure 12 and Table 3)

Table 3: Conditions for amide coupling (Approach 2, Figure 12)

Base	Solvent	Method <sup>a</sup>	Yield
DIPEA	DCM	17 h, rt	93%, crude UH-3
DIPEA	2-MeTHF (neat $\text{SOCl}_2$ in 1 <sup>st</sup> step)	22 h	no product
DBU	2-MeTHF	2 h, rt	37%
Tetramethylguanidine	2-MeTHF	36 h, rt	88%

Tetramethylguanidine worked well in 2-MeTHF but there is also a possibility for nitrosamine formation for tetramethylguanidine, but due to the D3.4 time limit it was not yet tested for nitrosamines.

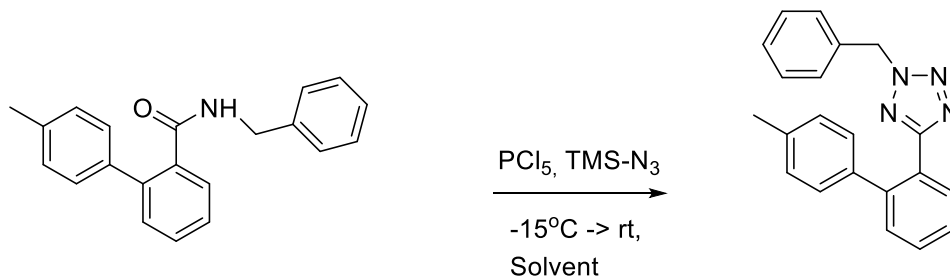


Figure 13: Second step of the synthesis

Table 4: Conditions of the tetrazole formation step

Entry	$\text{PCI}_5$ (Equiv.)	$\text{TMS-N}_3$ (Equiv.)	Solvent	Yield %
1	1	1	2-MeTHF	0%, only 100 mg scale
2	1.1	1.5	DCM	32%, 200 mg scale
3	1.1	1.5	DCM	90%, 800 mg scale
4	1.1	1.5	<i>n</i> -heptane/2-MeTHF	16%, solubility issue
5	1.1	1.5	2-MeTHF	0%, solubility issue
6	1.1	1.5	MeCN	11%

The tetrazole formation step (Figure 13, Table 4) was done by adding the  $\text{PCl}_5$  in portions during 20 min to the solution of *N*-benzyl-4'-methyl-[1,1'-biphenyl]-2-carboxamide in DCM, 2-MeTHF, *n*-heptane or MeCN at -12- -15 °C. There was a solubility issue with 2-MeTHF and *n*-heptane. The mixture was allowed to warm to rt and TMS- $\text{N}_3$  was added at -10 °C and stirred at rt overnight. A slight excess of azide is required for the formation of the tetrazole, often three equivalents are used.

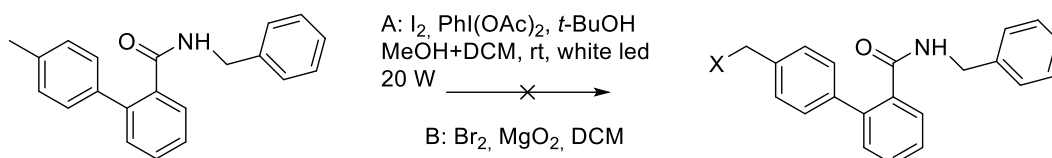


Figure 14: Halogenation attempts using model compound for the third step of the synthesis

Originally bromination of the benzylic methyl was done by DBDMH (1,3-dibromo-5,5-dimethyl hydantoin) using azobisisobutyronitrile (AIBN) as initiator, followed by nucleophilic displacement using 2-butyl-4-chloro-1*H*-imidazole-5-carbaldehyde and  $\text{K}_2\text{CO}_3$  in *N,N*-dimethyl acetamide. In this step originally carbon tetrachloride was used, and the plan was to avoid it. This step is not crucial for the formation of possible nitrosamines. *N*-benzyl-4'-methyl-[1,1'-biphenyl]-2-carboxamide was used as a model compound in this step due to the better availability of it than tetrazole. However, the attempts to halogenate the benzylic methyl failed. Photocatalytic iodination method A failed, and solubility of *N*-benzyl-4'-methyl-[1,1'-biphenyl]-2-carboxamide was poor to alcohols so additional DCM needed to be used. Also, bromination method B with bromine and MgO failed. This step requires more optimization.

## 6 ANALYSIS OF THE RESULTS

### Nitrosamine analysis:

**Analysis results** Rijksinstituut voor Volksgezondheid en Milieu, Bilthoven, the Netherlands (RIVM)

The samples have been analysed by liquid chromatography-mass spectrometry (UPLC-QTRAP-MS/MS) between the dates of 31-10-2024 and 16-12-2024 according to Ph. Eur. 2.5.42. *N-Nitrosamines in active substances* (method A (note that this is a limit test, not a quantification)) [10]. The method is slightly modified and due to the limited sample amount not additionally validated. The results can therefore only serve as an indication of the presence of NDiPA. The results are given below.

Table 5: Summary of analysis results.

Order#	NDiPA detected?
A229401 (UH-3)	Yes
A229402 (UH-2)	No
A229403 (UH-1)	No

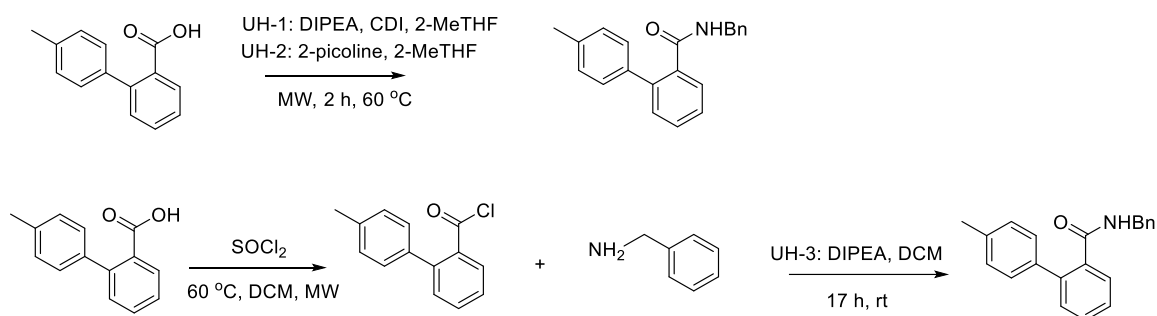


Figure 15: UH-1–UH-3 experiments.

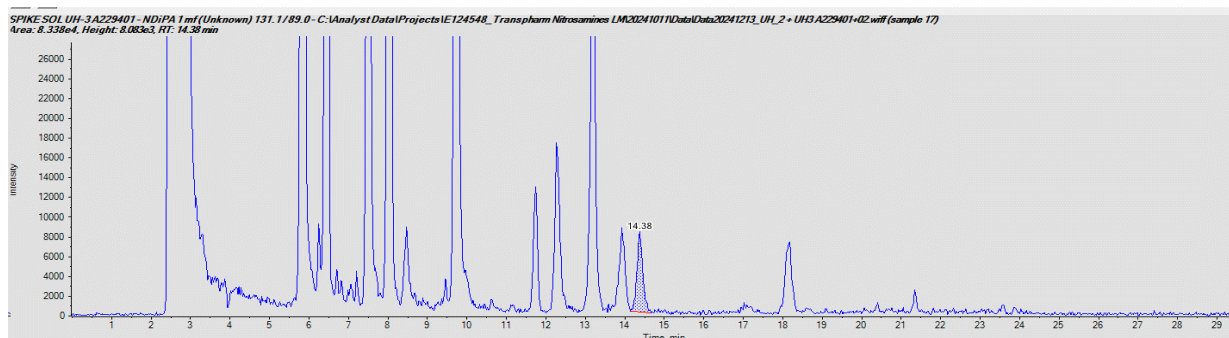


Figure 16: LC-MS chromatogram of NDIPA-spiked solution of sample AH229401 (UH-3)

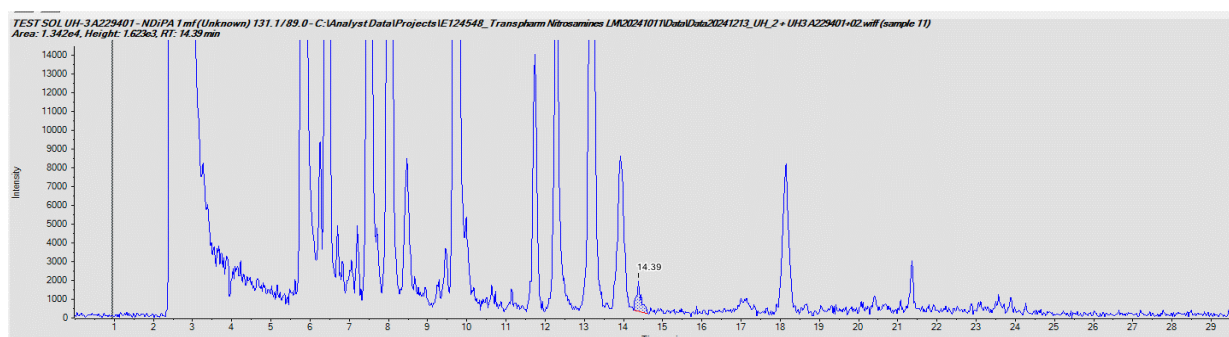


Figure 17: LC-MS chromatogram of sample AH229401 (UH-3)

Figure 16 and Figure 17 show that NDIPA (peak at 14.38/9 min) is formed in the reaction from DIPEA, and it is possible to detect from the complex crude mixture. This is a control reaction to monitor to typical conditions. UH-3 reaction was a two-step reaction; first the acid chloride is formed using  $\text{SOCl}_2$  in DCM and then overnight amide coupling using DIPEA in DCM (Table 3). In this reaction acidity can be present from DCM or  $\text{SOCl}_2$ .

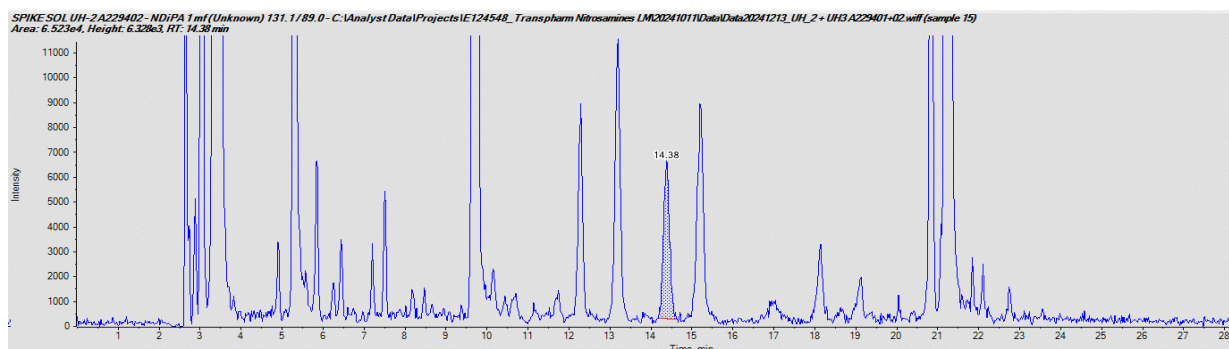


Figure 18: LC-MS chromatogram of NDIPA-spiked solution of sample AH229402 (UH-2)

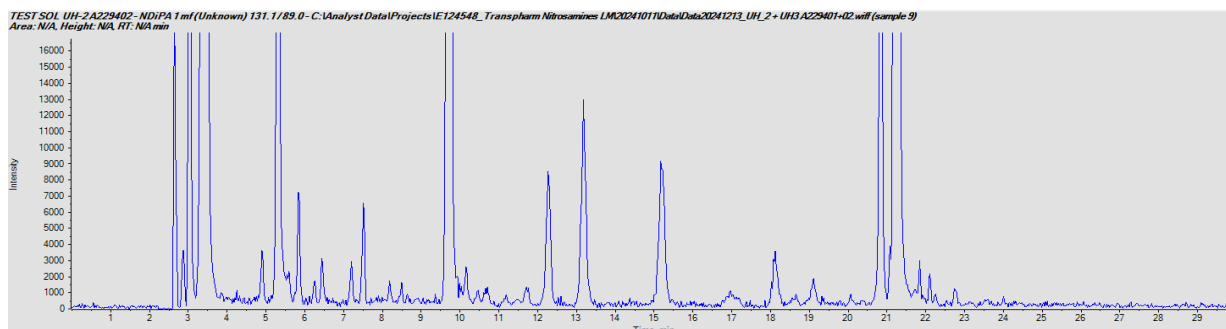


Figure 19: LC-MS chromatogram of sample AH229402 (UH-2)

In the experiment UH-2 (Table 2) 2-picoline was used as a base instead of DIPEA and no NDiPA was monitored as expected.

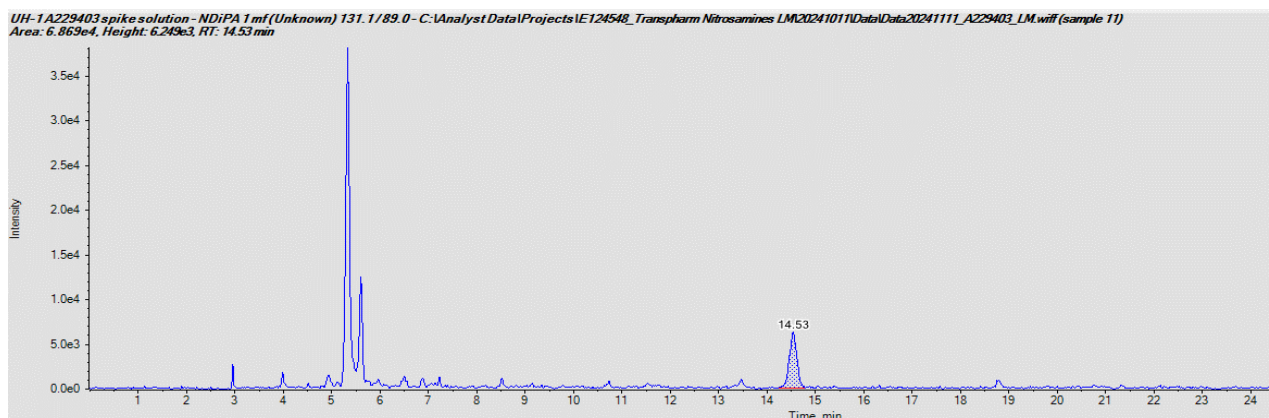


Figure 20: LC-MS chromatogram of NDiPA-spiked solution of sample AH229403 (UH-1)

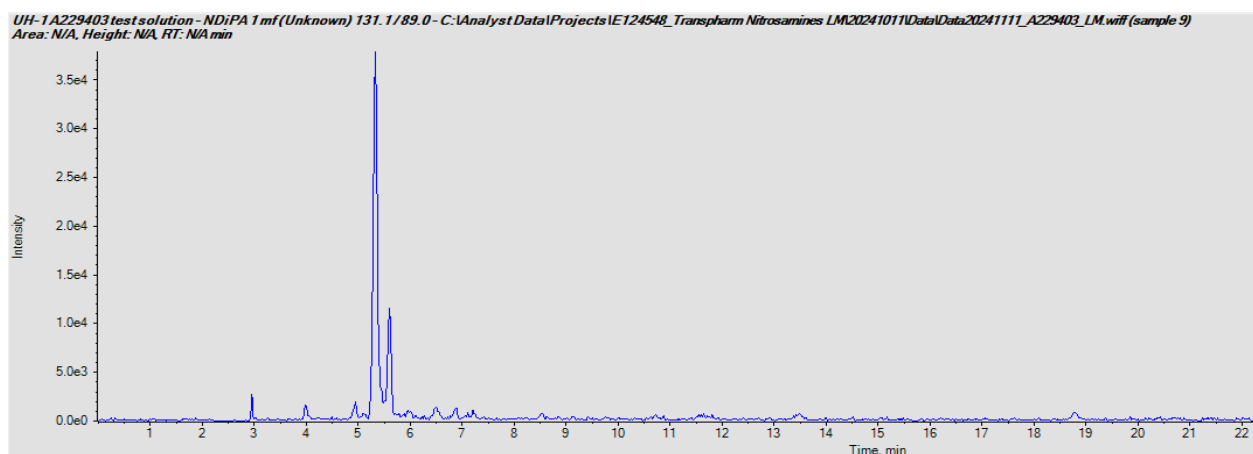


Figure 21: LC-MS chromatogram of sample AH229403 (UH-1)

The sample UH-1 conditions included DIPEA and 1,1'-carbonyldiimidazole (CDI) in 2-MeTHF, and no NDiPA was detected (Table 2). It is probably due to the short reaction time and lack of acidic conditions.

## 7 IMPACT OF THE RESULTS

- Improvement of irbesartan synthesis route to avoid formation of nitrosamines and usage of transition metals, also DCM can be replaced with a green solvent 2-MeTHF from renewable sources. We have shown that it is possible to detect nitrosamine e.g. NDEiPA impurities already at the early stage of the synthesis route from crude mixtures using Ph. Eur. analysis method.
- The developed  $C_6F_5BH_2 \cdot SMe_2$  is a highly efficient, metal-free hydroborylation catalyst for various C-C double bonds. It works excellently for both terminal and intramolecular alkenes. Whereas 9-BBN works well with ester functionalities,  $C_6F_5BH_2 \cdot SMe_2$  tolerates a very wide spectrum of different functional groups, such as halogens and TMS-protected alcohols. This has been demonstrated using several model substrates, including terpenes and steroids.

As we have shown here, the combination of metal-free hydroborylation and transborylation has proven to be a promising strategy for preparing air- and moisture-stable pinacolboranes. This scalable method addresses the need to develop a robust synthesis protocol for preparing boronic esters from simple, inexpensive alkenes for the pharmaceutical industry.

## 8 RELATED IPR

## 9 PUBLISHABLE INFORMATION

The metal-free experiments that were carried out and the results obtained, will be published as an article: *Slesarchuk N., Doerksen G., Vasko P., Repo T. Submitted, 2025*

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## 10 CONCLUSION

Implement control measures to mitigate nitrosamine and transition metal contamination.

Guidelines for reduction of nitrosamine and transition metal contamination:

- Optimize reaction conditions to minimize nitrosamine formation by controlling the time, temperature and pH (by avoiding the sources of acids), and transition metal introduction.
- Analyze the intermediates from nitrosamines based on the amines used in the reactions (there are many nitrosamine standards commercially available) and avoid using amine bases in DCM, replace it with e.g. green solvent 2-MeTHF and avoid acidic conditions.

Catalytic and metal-free concepts such as FLPs are key to avoiding transition metal contamination. They can replace, as presented here, transition metal-based catalysts for the hydroborylation of alkenes and thus complement the synthetic chemist's toolbox. However, in these reactions, metal-free catalysts face a challenge due to their high Lewis acidity, and therefore, there is a need to protect Lewis basic functional groups. On the other hand, halogens as functional groups are very challenging for metal catalysts, while metal-free catalysts can easily cope with them. Here developed  $C_6F_5BH_2 \cdot SMe_2$  is a highly efficient, metal-free hydroborylation catalyst for various C-C double bonds. It works excellently for terminal and intramolecular alkenes and provides a straightforward pathway to air- and moisture-stable pinacol-boranes.

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